PATENT
Our Docket: P-IX 2947

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of
Watkins and Huse

Serial No: 09/203,768

Filed: December 2, 1998

For: TUMOR SPECIFIC HUMAN MONOCLONAL ANTIBODIES AND METHODS OF USE

Group Art Unit: 1642

Examiner: L. Helms

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By: _____
David A. Gay, Reg. No. 39,200

February 20, 2001
Date of Signature

Commissioner for Patents
Washington, D.C. 20231

RESPONSE TO OFFICE ACTION

Responsive to the Office Action mailed August 18, 2000, consideration of the following Remarks is respectfully requested.

AMENDMENTS

In the claims:

Please amend the claims as follows:

1. (Amended) A human monoclonal antibody or functional fragment thereof, comprising at least one Complementarity Determining Region (CDR) having substantially the amino acid sequence of a CDR of SEQ ID NO:2 or SEQ ID NO:4, wherein said antibody or functional fragment thereof binds a neoplastic cell or antigen thereof.

EXHIBIT 1

6. (Amended) A CDR or functional fragment thereof, comprising substantially the amino acid sequence of a CDR of SEQ ID NO:2 or SEQ ID NO:4, wherein said CDR or functional fragment thereof binds a neoplastic cell or antigen thereof.

Please add the following new claims:

--47. (New) The human monoclonal antibody or functional fragment of claim 1, further comprising a physiologically acceptable compound.

48. (New) The human monoclonal antibody of claim 1, wherein said human monoclonal antibody is purified.--

REMARKS

Claims 1-46 are pending in the above-identified application and are subject to a restriction requirement under 35 U.S.C. § 121. Claims 1-6 have been elected with traverse and are currently under examination. Claims 1-6 stand rejected under the first and second paragraphs of 35 U.S.C. § 112. Applicants submit that the claims are in condition for allowance as set forth below.

Claims 1-6 are currently under examination. Claims 1 and 6 have been amended above. New claims 47 and 48 have been added. Support for the amendments can be found throughout the application. Specifically, support for the amendments to claims 1 and 6 can be found, for example, on page 5, lines 22-26; page

15, lines 19-31; and page 34, lines 16-28. Support for new claim 47 can be found, for example, on page 28, line 19, through page 29, line 3. Support for new claim 48 can be found, for example, on page 21, lines 31-33. Accordingly, the amendments do not introduce new matter and entry thereof is respectfully requested.

Claims 1-6 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for the following reasons. Claims 1-6 are alleged to be indefinite for reciting the term "substantially" because it is not clear if the CDR comprises the entire sequence of SEQ ID NO:2 or 4. Additionally, claims 1-6 are alleged to be indefinite for reciting the phrase "amino acid sequence of a CDR" because three different CDR definitions are provided in the specification. Claims 1 and 3-6 are alleged to be indefinite for reciting the term "functional fragment" because it is not clear what function is defined. Finally, claim 1 is alleged to be indefinite for reciting the term "having." In this regard, the Office Action questions whether the term renders the claim open or closed ended.

Applicants respectfully traverse these rejections of the claims for the following reasons. In regard to the term "substantially," the claim recites "at least one CDR having substantially the amino acid sequence of a CDR of SEQ ID NO:2 or SEQ ID NO:4." As taught on page 16, line 10-21, of the specification, SEQ ID NO:2 and SEQ ID NO:4 encode the VH and VL variable regions respectively of the human monoclonal antibody produced by the LH11238 cell line. It is sufficiently clear that the recited variable regions contain three CDR sequences from the

guidance provided in the specification including, for example, on page 8, line 21, through page 9, line 23, where the structures of variable regions and CDRs is taught. Similarly, in light of the plain language of the claim, it is sufficiently clear, therefore, that the claimed antibody can contain one, two or three CDRs having substantially the same sequence as a CDR of SEQ ID NO:2 or SEQ ID NO:4.

Furthermore, an antibody having a CDR that was substantially the same as a CDR having the sequence of a CDR of SEQ ID NO:2 or SEQ ID NO:4 would have been sufficiently clear according to the teaching provided in the specification. In this regard, the specification teaches that a CDR having an amino acid sequence that is substantially the amino acid sequence of a specifically recited reference CDR sequence can be identified based on the sequence of the reference CDR and the function of an antibody containing the reference CDR. For example, the specification teaches on page 8, lines 5-16, that an amino acid sequence which is substantially the same as a CDR exhibits a considerable amount or extent of sequence identity when compared to a reference sequence and that an antibody having the sequence maintains its function of selectively binding a tumor-specific antigen. Such substantially similar sequences would have been identifiable based on well known methods of sequence comparison. Furthermore, binding to a neoplastic cell, or antigen thereof, would have been sufficiently clear from a comparison of binding activities of antibodies containing one or more of the specifically recited CDRs. Therefore, the specification reasonably apprises those skilled in the art of the metes and bounds of the recited CDRs.

Applicants further contend that the meaning of the phrase "amino acid sequence of a CDR" is sufficiently clear to identify a claimed antibody having at least one of the recited CDRs. Specifically, the canonical structure of a CDR has been defined with various nomenclatures including, for example, those of Kabat et al., Chothia et al. or MacCallum et al. as taught on page 8, line 21, through page 9, line 23 of the specification. As taught on page 9, lines 4-9, of the specification, the exact residue numbers which encompass a particular CDR will vary depending on the sequence and size of the CDR and can be routinely determined by one skilled in the art based on the sequences of the VH and VL regions of an antibody. Accordingly, one skilled in the art would have been able to identify the CDRs in the specifically recited VH and VL sequences.

Furthermore, as described above an antibody having a specific CDR can be identified according to its ability to bind to a neoplastic cell, or antigen thereof. The binding activity of the antibody produced from the LH11238 cell line, containing the VH and VL regions encoded by SEQ ID NO:2 and SEQ ID NO:4, is taught throughout the specification. For example, page 52, lines 19-24, teach that the LH11238 antibody can specifically bind to intact H3396, H3464, H3477, H3639, and H3723 carcinoma cell lines. Applicants contend that based on the sequences recited in the claims, and guidance provided in the specification regarding the structure and function of CDRs, claims 1-6 would have been sufficiently clear to allow one skilled in the art to identify the claimed antibody having at least one of the specifically recited CDRs.

Applicants contend that the term "functional fragment" as it is used in the claims is sufficiently clear in view of the guidance provided in the specification. The specification defines the term "functional fragment" on page 9, lines 24-31 as a portion of an antibody that retains activity such as binding activity or specificity. The specification also teaches on page 9, line 31, through page 11, line 30 a number of exemplary antibody fragments that are known to retain such functions including, for example, VL, Fd, Fv, Fab, $F(ab')_2$, Fab' scFv and Fc fragments. As described above, the specification teaches the function of the claimed antibody, or functional fragment thereof, having the recited CDRs including, for example, binding activity toward carcinoma cell lines. According to the definition of the term functional fragment and the binding function taught in the specification, the recited phrase "functional fragment" would have been clear and definite.

The term "having" in claims 1-6 is intended to have open meaning. The claims are sufficiently clear, when interpreted with open language and in view of the guidance provided in the specification as described above.

Claims 1-6 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement. The Examiner alleges that a functional fragment containing less than six CDRs or even a single CDR would not have binding function. The Examiner alleges that undue experimentation would be required to produce the invention and relies on Rudikoff et al., Panka et al., and Amit et al., in alleging that even minor changes within the variable regions would have an adverse effect on antigen binding

function. The Examiner relies on Adair et al., in further alleging that transfer of CDR regions alone to an antibody framework would not result in binding activity.

Applicants respectfully traverse the rejection of claims 1-6 under 35 U.S.C. § 112, first paragraph. In this regard, Applicants respectfully submit that one skilled in the art would have known that a fragment containing less than six CDRs or even a single CDR can contain binding function because it was well known at the time of filing that fragments containing less than six CDRs were capable of binding activity. For example, VH and VL fragments having binding function while retaining only 3 CDRs were known in the art at the time of filing. Ward et al., Nature 341:544-546 (1989), provided as Exhibit A, describes the production of VH domains, from lysozyme specific antibodies, that retain low nanomolar affinity for lysozyme. Specifically, Ward et al. describe on page 544, column 1, line 1-11, that isolated, monomeric VH domains of an anti-lysozyme antibody could bind lysozyme. The affinity was 19 nM as described on page 544, column 2, lines 2-4, and presented Table 1 on page 544. Ward et al. states on page 546, column 1, lines 7-10, that

> [t]he affinity of the VH domains (20 nM or $5x10^7$ M^{-1}) for lysozyme lies within the range expected for the affinities of monoclonal antibodies for protein antigens, and can be improved by site directed mutagenesis.

Therefore functional fragments of antibodies having fewer than 6 CDRs were known in the art at the time of filing.

Moreover, even single CDRs having binding affinity for antigens bound by the respective full length antibody were well known in the art at the time of filing. For example, Ditzel et al., J. Immunol. 157:739-749 (1996), provided as Exhibit B, describes a CDR-derived peptide that demonstrates specific binding to antigens of the full-length antibody. Specifically, on page 745, column 1, lines 8-19, Ditzel et al. describes the 21 amino acid PEPLNA3 peptide having substantially the sequence of the HCDR3 of the polyreactive Fab, Fab LNA3. Ditzel et al. continues on page 745, column 1, lines 19-32 stating that

> [t]he binding specificity of PEPLNA3, as tested in an ELISA against a panel of Ags, demonstrated the ability of the peptide to bind multiple Ags. . .increasing concentrations of PEPLNA3 were able to inhibit the binding of Fab LNA3 with an apparent affinity in the micromolar range.

In another example, Williams et al., Proc. Natl. Acad. Sci. USA 86:5537-5541 (1989), provided as Exhibit C, describes CDR fragments that bind to the same cell receptor bound by the full length antibody. Williams et al. describe on page 5538, in the paragraph spanning columns 1 and 2, that 17-18 amino acid peptides having substantially the sequence of the second CDR of the monoclonal antibody 87.92.6 VL region were able to inhibit lymphocyte proliferation under conditions in which the 87.92.6 antibody demonstrated inhibitory effects. Therefore, CDRs and functional fragments thereof having binding activity were known in the art at the time of filing.

Further, Applicants respectfully submit that CDRs are not required to be in their proper order or in context of their original framework to have binding function. It was well known at the time of filing that antibodies, and fragments thereof, having antigen binding activity could be produced by altering the order and context of the CDRs. For example, the procedure of CDR shuffling, which is based on the random ordering of CDRs, was well known in the art to produce functional antibodies, and fragments thereof, for example, in antibody engineering applications. An example of CDR shuffling is provided in Ditzel et al. which describes on page 742, column 1, line 10, through column 2, line 15, a number of antibody fragments produced by CDR shuffling that retain binding activity for the antigens of the parent antibody. Examples of transferring one or more CDR from one framework to another to produce functional antibodies, and fragments thereof, were also well known in the art at the time of filing. Specifically, humanization of antibodies by transferring one or more CDRs from non-human antibodies to human frameworks have produced antibodies with sufficient binding function to be used as diagnostic and therapeutic agents. Examples of functional antibodies having grafted CDRs are listed in Table 1 of Walsh, Nature Biotech. 18:831-833 (2000), provided as Exhibit D, and include ReoPro, Rituxan, Zenapax, Simulaect, Remicade, Synagis, Herceptin and Mabthera. Grafting of a single CDR was known in the art to produce functional antibodies, or functional fragments thereof, as described, for example, in Ditzel et al. Specifically, Ditzel et al. describe on page 742, column 1, line 16, through page 745, column 1, line 22, grafting of the HCDR3 of the LNA3 antibody into the tetanus toxoid binding Fab p313 so as to replace the existing HCDR3 and binding specificity. As

described by Ditzel et al. on page 744, columns 1 and 2 the monospecific binding pattern of the p313 antibody was changed to a polyreactive binding pattern by grafting only the HCDR3 of LNA3 into the Fab. Therefore, antibodies and fragments thereof having CDRs grafted into non-native frameworks were known in the art to have binding activity.

Applicants contend that the full scope of the claimed invention is enabled by the specification even in view of the references cited in the Office Action. Amit et al. describes the crystal structure of an antibody in which framework residues are within hydrogen bonding distance of bound antigen. However, Amit et al., does not describe the framework residues as necessary for binding. Specifically, there is no demonstration that absence of the framework residue would have any effect on binding activity. Therefore, Amit et al. does not support the assertion in the Office Action that framework residues are required for binding activity.

Applicant contends that according to the guidance provided in the specification one skilled in the art would have been able to make and use functional fragments of the claimed antibodies lacking adverse mutations such as those described by Rudikoff et al., Panka et al. and Adair et al. For example, as described previously, one skilled in the art would have been able to determine the location of the CDRs in the specifically recited sequences based on the guidance provided in the specification. Accordingly, one skilled in the art would have been able to produce fragments lacking mutations in the CDRs thereby avoiding the adverse effects of the type reported in the cited references.

Moreover, even functional fragments having amino acid changes in one or more CDR could have been produced by the routine methods taught in the specification and described below.

Routine methods for making functional fragments of antibodies are taught throughout the specification including, for example, on page 23, line 8, through page 25, line 33, which teaches that fragments can be produced by proteolytic methods, recombinant methods and chemical synthesis. Fragments can be engineered for optimal properties such as affinity, selectivity, avidity, stability or bioavailability using routine methods such as those taught on page 26, line 1, through page 27, line 25 of the specification. Functional fragments produced by the methods taught in the specification could have been identified by routine methods taught in the specification. For example, functional fragments produced by protein engineering methods could be identified by the binding assays taught on page 50, line 27, through page 52, line 33 or page 53, line 1, through page 54, line 21. Therefore, according to the guidance provided in the specification, one skilled in the art would have been able to make and use functional antibody fragments.

Applicants contend that the full scope of the claimed invention is enabled because functional fragments of antibodies were expected in the art and the specification provides sufficient guidance for one skilled in the art to make and use the claimed functional fragments. Accordingly, Applicants request that this ground for rejection be removed.

Claim 5 stands rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement because there is insufficient guidance for using the claimed pharmaceutical compositions for the treatment of cancer. In this regard, the Office Action alleges that the use of antibodies for cancer therapy is unpredictable and undeveloped.

Applicants respectfully traverse the rejection of claim 5 under 35 U.S.C. § 112, first paragraph. Applicants respectfully disagree with the assertion that the art of cancer therapy with pharmaceutical compositions of antibodies is unpredictable. As described in Walsh (Exhibit D), the treatment of cancer with pharmaceutical composition is a developed art having achieved both commercial and medical success. Walsh describes on page 832, column 3, lines 27-29, that 31 monoclonal antibody-based products are in clinical trials for cancer. Furthermore Table 1 of Walsh lists 18 monoclonal antibody-based products that have been approved for medical use in the US or EU. Of these products at least four have been approved for cancer therapy including OncoScint CR/OV for the treatment of colorectal and ovarian cancers, Rituxan for the treatment of non-Hodgkin's lymphoma, Herceptin for the treatment of metastatic breast cancer, and Mabthera for the treatment of non-Hodgkin's lymphoma. This level of success in the clinic contradicts the assertion in the Office Action that the use of antibodies to treat cancer is unpredictable or undeveloped. Absent evidence to the contrary, the assertion that pharmaceutical compositions comprising antibodies are not useful for cancer is unfounded.

In view of the developed state of the art, the guidance provided in the specification would have sufficiently enabled one skilled in the art to make and use the claimed pharmaceutical composition. Specifically, the methods taught on page 28, line 12, through page 29, line 7, for making the claimed pharmaceutical compositions would have been routine. One skilled in the art would have been able to determine an effective amount of antibody, or functional fragment thereof, for the claimed composition based on the guidance provided in the specification, for example, on page 30, line 14, through page 32, line 2, which teaches routine methods for determining dose based on *in vivo* and *in vitro* tests and/or characteristics of the individual to be treated. In accordance with the developed state of the art of antibody-based cancer therapy, one skilled in the art would have been capable of producing the claimed pharmaceutical compositions and evaluating the efficacy of the compositions according to the routine methods taught in the specification. Therefore, the claimed pharmaceutical compositions are enabled by the specification. Accordingly, Applicants request that this ground for rejection be removed.

CONCLUSION

In light of the Amendments and Remarks herein, Applicants submit that the claims are now in condition for allowance and respectfully request a notice to this effect. Should the Examiner have any questions, he is invited to call the undersigned agent or Cathryn Campbell.

Respectfully submitted,

February 20, 2001
Date

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